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Use of combination therapy in asthma: Are they prescribed according to guidelines ☆

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Summary
Background: Combination therapy should be prescribed to patients with moderate to severe asthma after daily long-term treatment with inhaled inhaled corticosteroids (ICS) has been tried without obtaining adequate control and it is not indicated to be used as first line treatment in asthma.
Objectives: To describe the use of combination therapy for the treatment of asthma and to evaluate to which extent it is prescribed as recommended.
Methods: A cohort of 14 559 new users of a combination therapy identified between January 1, 2000 and September 30, 2003 was selected from beneficiaries of the Régie de l'assurance maladie du Québec. We evaluated whether the combination therapy was prescribed according to the Canadian Asthma Guidelines. A logistic regression analysis was also performed to identify patient's and physician's characteristics associated with the adherence to the recommendations of the Canadian Asthma Guidelines for the prescription of a combination therapy.
Results: Only 40% of users of combination therapy filled a prescription of ICS in the year preceding the initiation of the therapy and this proportion decreased by 21.8% from 2000 to 2003. Patients who received their first combination therapy in an emergency department were less likely to have used ICS previously, but patients treated by a respiratory physician and patients with co-morbidities, markers of asthma severity and markers of uncontrolled asthma were more likely to have used ICS previously.

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Conclusion: Combination therapy has not been used according to the Canadian Asthma Guidelines in a large proportion of patients.

Introduction

Current evidence indicates that daily long-term control medications are necessary to prevent exacerbations and chronic symptoms for all patients with persistent asthma, whether asthma is mild, moderate, or severe.[1–3] According to Canadian and International Guidelines (GINA) for asthma management, inhaled corticosteroids (ICS) are preferred because they are the most effective anti-inflammatory medication available for treating the underlying inflammation characteristic of persistent asthma.[1–3]

A stepwise approach is recommended for the treatment of asthma based on the underlying severity of symptoms.[1–4] When asthma is not optimally controlled with ICS alone, the addition of long-acting β_2-agonists (LABA) to ICS is recognised as the most effective therapy to control moderate to severe asthma.[2] On the other hand, LABA should not be used in monotherapy and should not be initiated before a treatment with ICS has been tried.[2]

Two medications, ICS and LABA, have been combined into one inhaler (combination therapy): salmeterol plus fluticasone and formeterol plus budesonide. Combination therapy should be prescribed to patients with moderate to severe asthma after daily long-term treatment with ICS has been tried without obtaining adequate control and it is not indicated to be used as first line treatment in asthma.[5] To our knowledge no study has described the use of combination therapy for the treatment of asthma in real clinical practice.

The purpose of this study was to describe the use of combination therapy for the treatment of asthma and to evaluate to which extent it is prescribed as recommended, i.e. after ICS in monotherapy have been tried. We also investigated patient's and physician's characteristics associated with adherence to guidelines' recommendations.

Methods

Source of data

This study was based on data retrieved from the administrative databases of the Régie de l'assurance maladie du Québec (RAMQ). These databases contain claims data on health care services provided to Quebec residents. With unique encrypted health insurance number, the four following databases administered by the RAMQ were merged at the patient level: drug plan admissibility, beneficiary information, prescription and medical services claims. The Medical Services Database includes residents covered by the provincial health care insurance (essentially the whole population of Québec) and the Prescription Drug Database includes residents covered by the RAMQ drug insurance plan, which represents about 43% of the total population of Québec.[6] In 2002, this drug plan was covering 3 154 465 people classified into three groups: welfare recipients (545 651 individuals), seniors of 65 years old or more (883 483 individuals), and people under 65 years old who do not have access to a private group insurance (1 725 331 individuals).

The RAMQ databases provide also socio-demographic information such as age, gender, receipt or not of social assistance, area of residence and date of death, when applicable. The drug plan admissibility database provides information on the duration of the admissibility to the RAMQ drug insurance plan. For all prescription drugs dispensed to beneficiaries of the RAMQ drug plan, the Prescription Drug Database contains information such as the unique patient's identifier, drug name, dose, dosage form, quantity of drug dispensed, prescription duration, prescription dispensation date and the specialty of the prescribing physician. For each medical service dispensed, the Medical Services Database contains information on the date and place where it was dispensed (hospital, emergency department [ED], or medical clinic), the ICD-9 diagnosis code, the specialty, year and place of graduation of the treating physician and the unique patient's identifier. The accuracy of the RAMQ prescription claims database as a source of information on drug use in pharmacoepidemiological research has been established.[7]

Study cohort

This study was based on a cohort of new users of combination therapy aged between 16 and 44 years old selected from the RAMQ databases between January 1, 2000 and September 30, 2003. To enter the cohort, patients had to fulfill the following criterion: (1) having at least one prescription of a combination therapy filled between January 1, 2000 and September 30, 2003 (the first prescription filled on or after January 1, 2000 will be referred to as the index date); (2) being aged between 16 and 44 years old on the index date; (3) being covered by the RAMQ drug plan for at least one year prior to the index date; (4) filled no prescription of a combination therapy for at least one year preceding the index date; (5) filled no prescription for acetylcysteine, epinephrine racemique, ipratropium bromide, ipratropium bromide/salbutamol, ipratropium bromide/fenoterol, morphine, pancrelipase, pancreatin, tobramycin injectable in the year preceding the index date, as an attempt to eliminate patients with COPD and cystic fibrosis. During the years 2000–2002 only the salmeterol/fluticasone combination product (Advair) was reimbursed by the RAMQ drug plan and in 2003 both products (Advair and Symbicort (formeterol/budesonide)) were reimbursed by the RAMQ. However, patients who initiated a treatment with a combination therapy (Symbicort only, Advair was on the regular list) between November 2002 and January 2003 were excluded since during that period combination products were removed from the regular

list of medications of the RAMQ and could be prescribed only under certain restricted conditions.

Patients entered the cohort on the date of the first prescription of a combination therapy filled on or after January 1, 2000 (index date). Data on prescription and medical services were obtained from the RAMQ for all cohort members for the period between January 1st 1999 and September 30, 2003.

Adherence to prescribing recommendations

Main criteria

Patients were considered adherent to the recommendations[1,2] if they filled at least one prescription of an ICS in the year preceding the filling of the first prescription of a combination therapy (index date).

Strict criterion

In a second analysis, patients were considered adherent with the recommendations if they used ICS regularly (i.e. at least 75% of the time) in the year preceding the index date. To assess this criterion the duration of each prescription of ICS filled in the year preceding the index date was summed. The percentage of time with an ICS therapy was then categorized: 0%; $>$0–25%; $>$25–50%; $>$50–75%; $>$75% of the time.

Factors associated with non-adherence

We investigated whether pre-defined patient's and physician's characteristics were associated with adherence (according to the main criteria) to recommendations for the prescription of combination therapy.

Patient's characteristics

The patient's characteristics under study were regrouped into four categories. First, socio-demographic variables including age at index date, gender, region of residence (rural/urban), receipt of social assistance (yes/no) and number of co-morbidities. A patient was identified as having a co-morbidity if he or she filled at least two prescriptions of a medication indicated to treat a chronic disease. Cardiovascular disease (CVD), cancer, epilepsy, CNS disease, anxiety and depression, gastrointestinal disease and diabetes were considered in the analysis.

Second, variables associated with the prescription of the combination therapy included the year of treatment initiation, the daily dose of ICS in the first prescription ($\leqslant$250 versus $>$250 mcg per day in fluticasone equivalent), and the place where the combination therapy was first prescribed (medical clinic, ED, hospital or other).

Third, variables related to the treatment of asthma in the year preceding the index date included the presence or absence of an asthma diagnosis recorded in the RAMQ database, the use of oral corticosteroids (yes/no), the use of LABA (yes/no) and the average number of doses of short-acting inhaled β_2-agonist per week (0, $>$0–3, $>$4–10, $>$10 doses). To calculate the mean weakly doses of short-acting inhaled β_2-agonist we developed an algorithm on the basis of the name and formulation of the product prescribed, prescription renewals, quantity of medication dispensed, duration of the prescription, and length of time between renewals. Equivalencies between the different medications dispensed were assessed by a clinical pharmacist specialized in respiratory health.[8]

Fourth, variables related to the use of health care services in the year preceding the index date included ED visit for asthma (yes/no), hospitalization for asthma (yes/no) and the filling of an antibiotic prescription at plus or minus five days from the index date (yes/no).

Physician's characteristics

The characteristics of the physician who prescribed the combination therapy on the index date were investigated. The variables under study were the specialty of the treating physician (respiratory physician, family physician and other specialists), and the year and university of graduation.

Statistical analyses

Main analyses

We first estimated the proportion of patients with a new combination therapy who fulfilled the main criterion of adherence to the recommendations. We also estimated the proportion of patients with a new combination therapy who fulfilled the strict criterion of adherence. This analysis was restricted to patients who were covered by the RAMQ drug plan for at least one year prior to the index date in order to account for prescriptions of ICS filled before the year preceding the index date but used during that year. In addition, we estimated the proportion of patients who filled at least one prescription of a short-acting inhaled β_2-agonist, a LABA and any medication indicated in the treatment of asthma (ICS, LABA, short-acting β_2-agonist, theophylline or anti-leukotriene) in the year preceding the index date. The precision of these estimates was assessed with 95% confidence intervals. These proportions were estimated separately for the years 2000–2003 in order to investigate the presence of a trend over time.

Finally, a logistic regression analysis was performed to identify patients' and physicians' characteristics associated with the adherence to the recommendations for the prescription of a combination therapy (main criterion).

Sensitivity analyses

Two sensitivity analyses were performed to validate the robustness of our criterion for adherence. For the first sensitivity analysis, the main criterion was applied over a period of two years prior to the index date. A patient was thus considered having a treatment in adherence to the recommendations if he or she filled at least one prescription of ICS in the two years preceding the index date. This analysis was restricted to patients who were covered by the RAMQ drug insurance plan for at least two years prior to the index date and did not receive any prescription of a combination therapy during the same period. For the second sensitivity analysis, the estimation of the proportion of patients in adherence with the recommendations was restricted to patients who had at least one asthma diagnosis in the year prior to the index date.

Results

We initially identified 85 393 patients aged 16 years old or more from the RAMQ databases who filled at least one prescription of a combination therapy from January 1, 2000 to September 30, 2003. We then selected the patients who were aged between 16 and 44 years old when they filled their first prescription of a combination therapy. From these 19 456 patients, we excluded 3850 patients because they had less than a year of RAMQ drug coverage before the index date and 942 subjects because they filled at least one prescription of a medication indicated for COPD or cystic fibrosis in the year preceding the index date. We also excluded 105 patients because they received their first prescription of a combination product between November 2002 and January 2003 while this medication was on the restricted *List of medications of* Québec. The cohort of new users of a combination therapy was thus formed of 14 559 patients.

Table 1 shows the patients' characteristics prior to the first prescription of a combination therapy. Forty-six percent of the patients were aged between 35 and 44 years old, 37.1% were male, 40.4% were receiving social assistance and 0.8% had more than 5 co-morbidities. The vast majority of the patients (93.0%) started their combination therapy with a dose of ICS larger than 250 mcg per day in fluticasone equivalent and 74.1% of patients had their first combination therapy prescribed in a medical clinic. Only half of the patients (51.7%) had an asthma diagnosis recorded in the RAMQ database in the year preceding the index date. Regarding asthma treatment, we observed that 8.5% filled at least one prescription of oral corticosteroids, 20.4% took more than 10 doses per week of short-acting β_2-agonists, less than 1% had LABA without ICS, 9.0% had an emergency visit for asthma and 1.6% were hospitalized for asthma in the year preceding the index date.

The use of ICS in the year preceding the first prescription of a combination therapy is presented in Table 2. We observed, overall, that 39.6% of patients filled at least one prescription of an ICS in the year preceding the first prescription of a combination therapy. We also observed that this proportion decreased over time, being 55.0% in 2000 and 33.2% in 2003. We observed the same phenomenon for all the other asthma medications under study.

The results of the analysis of the determinants of the use of ICS prior to the index date are presented in Table 3. The logistic regression model ($n = 14\,559$) revealed that patients aged between 25 and 34 years old were less likely to use ICS prior to the index date, while patients receiving social assistance and patients having two co-morbidities or more were more likely to use ICS prior to the index date. We also observed that patients were progressively, over calendar time, less likely to have used ICS prior to the first prescription of a combination therapy. Patients who received their first combination therapy in an ED were less likely than others to have used ICS previously, while patients who initiated their combination therapy with 251 mcg per day or more of ICS (in fluticasone equivalent) and patients who had their combination therapy prescribed by a respiratory physician were more likely to use ICS prior to the index date. Moreover, we observed that patients who had a diagnosis of asthma and patients with markers of uncontrolled or severe asthma in the year preceding the initiation of the combination therapy, such as the use of oral corticosteroids, LABA and an ED visit for asthma, were more likely to have used ICS prior to the combination therapy. Finally, we found that patients who had more than one prescribing physician were more likely while patients who filled a prescription for an antibiotic on or close to the index date were less likely to have used ICS previously.

In order to further study the use of ICS preceding the first prescription of a combination therapy, we estimated the proportion of patients using ICS regularly (75% of the time or more). For the years 2000–2003 combined, we observed that only 2.5% of patients used ICS more than 75% of the time, 38.9% used ICS less than 75% of the time and 58.6% had not filled any prescription of ICS in the year preceding the index date.

Table 1 Patients' characteristics prior to the first prescription of a combination therapy ($n = 14\,559$).

	Number (%)
Socio-demographic variables	
Age (years)	
16–24	3108 (21.3)
25–34	4713 (32.4)
35–44	6738 (46.3)
Male	5402 (37.1)
Living in urban area	11 275 (77.4)
Receiving social assistance	5876 (40.4)
Number of co-morbidities	
<5	14 437 (99.2)
$\geqslant 5$	122 (0.8)
1st prescription of a combination therapy	
Years	
2000	1836 (12.6)
2001	3881 (26.7)
2002	5070 (34.8)
2003	3772 (25.9)
Dose of ICS (mcg per day in fluticasone equivalent)	
>250	13 546 (93.0)
Site of prescription	
Clinic	10 787 (74.1)
ED	1323 (9.1)
Hospitalisation	252 (1.7)
Other	2197 (15.1)
Asthma related variables in the year preceding the index date	
$\geqslant 1$ asthma diagnosis	7527 (51.7)
$\geqslant 1$ prescription of oral corticosteroids	1231 (8.5)
Short-acting β_2-agonist (number of doses per week)	
0	8634 (59.3)
>0–10	2956 (20.3)
>10	2969 (20.4)
$\geqslant 1$ ED visit for asthma	1314 (9.0)
$\geqslant 1$ hospitalisation for asthma	227 (1.6)
LABA without any form of ICS	137 (0.9)

Table 2 Use of asthma medications in the year preceding the first prescription of a combination therapy (index date).

	Year of first prescription of a combination therapy				
	2000	2001	2002	2003	2000–2003
Number of patients	1836	3881	5070	3772	14559
Patients with at least one dispensed prescription in percent [95% *CI*]					
ICS	55.0 [52.7; 57.3]	42.8 [41.3; 44.4]	36.3 [34.9; 37.6]	33.2 [31.7; 34.7]	39.6 [38.8; 40.4]
Short-acting β_2-agonist	62.7 [60.5; 64.9]	52.1 [50.5; 53.6]	45.6 [44.2; 46.9]	41.3 [39.7; 42.8]	48.4 [47.5; 49.2]
LABA	17.7 [16.0; 19.4]	8.3 [7.4; 9.2]	6.8 [6.1; 7.5]	9.7 [8.8; 10.7]	9.3 [8.9; 9.8]
Any asthma medication[a]	69.9 [67.8; 72.0]	58.7 [57.1; 60.2]	52.9 [51.6; 54.3]	49.7 [48.1; 51.3]	55.8 [55.0; 56.6]

[a]Asthma medications: ICS, SABA, LABA, anti-leukotriene, theophyllines and oral corticosteroids.

Table 3 Patients' and physicians' characteristics associated with the use of ICS prior to the first prescription of a combination therapy ($n = 14559$).

	% users of ICS	Adjusted OR	95% CI
Socio-demographic variables			
Age (years)			
16–24	39.8	Reference	
25–34	39.0	0.88	0.78; 1.00
35–44	39.8	1.01	0.90; 1.15
Gender			
Female	39.6	Reference	
Male	39.7	0.98	0.89; 1.08
Region of residence			
Urban	40.2	Reference	
Rural	37.5	1.03	0.92; 1.15
Social assistance			
No	35.5	Reference	
Yes	45.8	1.40	1.27; 1.55
Number of co-morbidities			
0	35.7	Reference	
1	43.1	1.03	0.91; 1.17
2–4	49.4	1.15	1.01; 1.32
5+	71.3	2.79	1.69; 4.61
1st prescription of a combination therapy			
Year			
2000	55.0	Reference	
2001	42.8	0.90	0.77; 1.05
2002	36.3	0.76	0.66; 0.88
2003	33.2	0.66	0.56; 0.79
Dose of ICS (mcg per day in fluticasone equivalent)			
$\leqslant 250$	29.1	Reference	
> 250	40.4	1.36	1.13; 1.64
Site of prescription			
Clinic	39.7	Reference	
ED	29.5	0.69	0.58; 0.82
Hospitalisation	55.6	0.74	0.52; 1.07
Other	43.6	1.23	1.09; 1.41
Asthma related variables in the year preceding the index date			
$\geqslant 1$ asthma diagnosis			
No	21.5	Reference	
Yes	56.4	2.04	1.85; 2.25

Table 3 (*continued*)

	% users of ICS	Adjusted OR	95% CI
$\geqslant$ 1 oral corticosteroids			
0	36.4	Reference	
$\geqslant$ 1 rx	73.8	1.27	1.07; 1.51
Short-acting β_2-agonists (number of doses per week)			
0	16.0	Reference	
$>$0–3	62.6	6.05	5.21; 7.01
$>$3–10	69.7	7.83	6.89; 8.89
$>$10	80.7	12.03	10.66; 13.58
LABA			
No	34.4	Reference	
Yes	89.9	10.11	8.21; 12.45
ED visit for asthma			
No	35.7	Reference	
Yes	79.1	1.71	1.42; 2.06
Hospitalisation for asthma			
No	38.9	Reference	
Yes	80.6	0.74	0.48;1.14
Number of prescribers			
0–1	16.7	Reference	
2	36.0	2.08	1.81; 2.39
+3	52.6	3.02	2.67; 3.43
Antibiotics ($\pm$5 *days around the index date*)			
No	44.0	Reference	
Yes	23.9	0.75	0.66; 0.84
Physician's characteristics			
Speciality			
Family physician	36.3	Reference	
Respiratory physician	70.4	1.58	1.32; 1.88
Other specialist	49.8	1.48	1.19; 1.84
Year of graduation			
69 or less	34.6	0.84	0.69; 1.01
70's	42.2	0.93	0.81; 1.07
80's	39.0	0.93	0.81; 1.07
90's or more	37.0	Reference	
Missing	48.9	1.36	0.93; 1.98
University of graduation			
Montreal	40.4	Reference	
Laval	37.5	0.97	0.86; 1.09
Mcgill	37.6	0.95	0.76; 1.17
Shebrooke	40.7	0.95	0.79; 1.14
Other Canadian or US universities	46.3	0.78	0.59; 1.02
Missing	40.9	0.97	0.85; 1.10

In the first sensitivity analysis we observed that 50.3% of patients ($n = 12\,732$) filled at least one prescription of an ICS within the two years preceding the index date, resulting in a 10% increase as compared with the primary analysis which was based on the year preceding the index date. We also observed in this sensitivity analysis that the percentage of patients using ICS prior to the index date decreased over time, from 65.1% in 2000 to 43.5% in 2003.

The second sensitivity analysis was performed among patients who had at least one diagnosis of asthma recorded in the RAMQ databases in the year preceding the index date. The percentage of patients using ICS found in this sub-group of 7527 patients was higher than those found in the first sensitivity analysis and the main analysis, with 56.4% of the patients who filled at least one prescription of an ICS in the year preceding the index date.

Discussion

The results of this study demonstrate that only 40% of new users of a combination therapy filled a prescription of ICS in

the year preceding the initiation of the therapy between 2000 and 2003. Another important finding of this study is that the percentage of patients using ICS prior to their first prescription of a combination therapy decreased by 21.8% from 2000 to 2003.

Even when we looked back two years prior to the initiation of a combination therapy we found that only 50% of the patients had filled a prescription of ICS prior to treatment initiation. These results show that combination therapies tend to be initiated for a large proportion of patients early in the course of the treatment for asthma and are not used as recommended by the Canadian Asthma Guidelines,[2] i.e. when asthma is not well controlled with a low to moderate dose of ICS. In this study, however, it is not possible to differentiate between patients who receive a prescription of ICS and did not fill it and patients who did not receive such a prescription. Even though the Canadian Asthma Guidelines are not clear on this issue, someone may argue that patients who present with moderate to severe asthma symptoms may benefit from combination therapy even if he or she did not use ICS previously. However, in our population, patients with markers of moderate to severe exacerbations (filled prescription of oral corticosteroids, emergency room visit and hospitalization for asthma) and no use of ICS prior to the initiation of the combination therapy represented only 5.5% of the patients who started a combination therapy.

We also performed an analysis to identify patients' and physicians' characteristics that might explain, at least in part, how the combination products were used or prescribed. From this analysis we found that patients aged between 25 and 34 years old were less likely to use ICS prior to their first prescription of a combination product. On the other hand, patients with markers of asthma severity and uncontrolled asthma prior to the initiation of the combination therapy were more likely to have used ICS previously. Moreover, we found that patients who receive their first prescription of a combination therapy in an ED or from a family physician and patients who did not receive a medical service for asthma in the year prior to the combination therapy, as well as patients who filled a prescription of antibiotics close to the date of their first prescription of a combination therapy were less likely to have used ICS previously. These findings might indicate that a non-negligible proportion of patients receive the combination therapy for an indication other than asthma and might explain the absence of a prescription of ICS prior to the filling of a combination therapy.

Having this study based on data retrieved from a large administrative database has several advantages. Firstly, we were able to reconstruct a large cohort of new users of combination therapy, providing precise estimates and high statistical power to identify determinants of adherence to guidelines for the prescription of a combination therapy. Secondly, the results of our study reflect the real clinical practice, avoiding a potential Hawthorne effect that could be present if prescribing physicians and patients would be aware that they were under examination.[9,10] Thirdly, by assessing medication use through prescription refills we avoided recall bias: the database provides prospectively collected full details on name, dose, and amount of drugs dispensed, information that is almost impossible to obtain by questionnaire after time has elapsed.[11,12]

This study has also a few limitations that should be taken into account in the interpretation of the results. Firstly, the RAMQ database provides information on welfare recipients and adherents to the RAMQ drug insurance plan only and not for residents who are covered by a private drug insurance. This led to a sample in which patients with high socio-economic status were under represented. Lower socio-economic status has been found to be associated with non-adherence to asthma guidelines,[1] and consequently we might have over estimated non-adherence to the guidelines. Secondly, the indication for which the combination therapy has been prescribed is unknown. Although combination therapy is only indicated for the treatment of asthma among patients aged less than 45, some patients might have received a combination therapy for another indication. In order to minimize this problem we performed a sensitivity analysis among patients who had a medical service for asthma in the year preceding the first prescription of a combination therapy. This analysis showed us that the percentage of patients who used ICS previously increased by about 16%, but despite this increase only 56% of the patients had filled a prescription of ICS in the year preceding the initiation of the combination therapy. Finally, as discussed previously, due to the nature of the prescription database, it is not possible to differentiate between patient's behaviour and physician's prescribing habits. The absence of a filled prescription of ICS prior to the first prescription of a combination product can be due either to a patient that did not fill a prescription of ICS or to the fact that the physician prescribed a combination product as the initial long-term control asthma medication. Another explanation for the absence of a filled prescription of ICS prior to the combination therapy is the patient receiving samples of ICS medications from his treating physician before he decides to prescribe a combination therapy.

The results of this study show that combination therapy has not been used according to the Canadian Asthma Guidelines in a large proportion of patients. Prior markers of asthma severity and uncontrolled disease were, as expected, found to be associated with guidelines' adherence, but a non-negligible proportion of patients treated with a combination therapy had no medical service for asthma, had very mild asthma or received a combination product as the initial controller therapy for asthma. Increasing patients' and physicians' education about the place of combination therapy in the treatment of asthma might increase guidelines' adherence. Education programs could focus on patients treated in family medicine clinics and in emergency departments in which non-adherence to guidelines has been found to be more prevalent.

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